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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/539,845

02/09/2006

Rudolf-Giesbert Alken

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23685 7590 09/02/2009

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EXAMINER

VALENROD, YEVGENY

ART UNIT

PAPER NUMBER

1621

MAIL DATE

DELIVERY MODE

09/02/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/539,845	Applicant(s) ALKEN, RUDOLF-GIESBERT	
	Examiner YEVEGENY VALENROD	Art Unit 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 June 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-10 and 34-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-10 and 34-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/22/09 has been entered.

Amendment to the claims filed 6/22/09 is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-6 and 34-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiesi (US 5,017,607) in view of Kushner et al., (Canadian Journal of Physiology and Pharmacology (1999), 77(2), 79-88).

Scope of prior art

Chiesi teaches a method of treating Parkinson's disease and neurological syndromes connected with it by administration of the methyl ester of levodopa combined with other active ingredients including carboxylase and monoaminoxidase inhibitors (abstract). As such the teaching of Chiesi is taken to teach both levodopa methyl ester, pharmaceutical compositions comprising levodopa and method treating Parkinson's.

Ascertaining the difference between prior art and instant claims

Although levodopa methyl ester of Chiesi comprises deuterium at its natural abundance, Chiesi fails to teach deuterated ester of levodopa as recited in the instant claims.

Secondary reference

Kushner discloses that it is advantageous to deuterate pharmaceutical compounds because isotopic enhancement of known drugs leads to enhancement of efficacy of known pharmaceuticals by improving the activity and increased duration of actions compared to the non-deuterated (non-isotopically enhanced) known drugs.

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Kushner describes that the deuterated forms of drugs often have different actions than the protonated forms. Some deuterated drugs show different transport processes. Most are more resistant to metabolic changes, especially those changes mediated by cytochrome P 450 systems. Deuteration may also change the pathway of drug metabolism (metabolic switching). Changed metabolism may lead to increased duration of action and lower toxicity. It may also lead to lower activity, if the drug is normally changed to the active form *in vivo*. Deuteration can also lower the genotoxicity of therapeutic compounds. Deuteration increases effectiveness of compounds by preventing their breakdown by target microorganisms. See page 83+.

Obviousness

The issue at hand is whether one skilled in the art at the time the instant invention was made would have found it obvious to prepare deuterated version of the methyl ester of levodopa and to utilize it in treatment of Parkinson's disease.

One skilled in the art would have found it obvious to prepare the deuterated versions of the methyl ester of levodopa. Levodopa is a well known drug that is widely utilized for treatment of neurological diseases including Parkinson's and restless leg syndrome. There is inherent motivation to improve on the bioavailability, activity and efficacy of the LDOPA and its prodrugs (methyl ester is a prodrug of LDOPA). Kushner teaches that such improvements can be attained by preparing deuterated versions of the known drugs.

In this regard, based on Kushner, those of ordinary skill would have been motivated to prepare those deuterated species that are instantly claimed, since these

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compounds would predictably have enhanced efficacy, activity, bioavailability and duration of action. Therefore, the instantly claimed deuterated compounds are prima facie obvious. Pharmaceutical compositions and the method of using the instant compounds are also obvious. One skilled in the art would find it obvious to use the deuterated variant of LDOPA prodrug to perform the same treatment as is already practiced with protonated variant.

Claims 2-5, 7-10 and 34-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milman et al (US 5,525,631) in view of Kushner et al., (Canadian Journal of Physiology and Pharmacology (1999), 77(2), 79-88).

Scope of prior art

Milman teaches a method of treating Parkinson's disease and neurological syndromes connected with it by administration of the ethyl ester of levodopa combined with other active ingredients including carboxylase and monoaminoxidase inhibitors (abstract; column 3, lines 48-55). As such the teaching of Milman is taken to teach both levodopa ethyl ester, pharmaceutical compositions comprising levodopa and method treating Parkinson's.

Ascertaining the difference between prior art and instant claims

Although levodopa ethyl ester of Milman comprises deuterium at its natural abundance, Milman fails to teach deuterated ester of levodopa as recited in the instant claims.

Secondary reference

Kushner discloses that it is advantageous to deuterate pharmaceutical compounds because isotopic enhancement of known drugs leads to enhancement of efficacy of known pharmaceuticals by improving the activity and increased duration of actions compared to the non-deuterated (non-isotopically enhanced) known drugs. Kushner describes that the deuterated forms of drugs often have different actions than the protonated forms. Some deuterated drugs show different transport processes. Most are more resistant to metabolic changes, especially those changes mediated by cytochrome P 450 systems. Deuteration may also change the pathway of drug metabolism (metabolic switching). Changed metabolism may lead to increased duration of action and lower toxicity. It may also lead to lower activity, if the drug is normally changed to the active form *in vivo*. Deuteration can also lower the genotoxicity of therapeutic compounds. Deuteration increases effectiveness of compounds by preventing their breakdown by target microorganisms. See page 83+.

Obviousness

The issue at hand is whether one skilled in the art at the time the instant invention was made would have found it obvious to prepare deuterated version of the ethyl ester of levodopa and to utilize it in treatment of Parkinson's disease.

One skilled in the art would have found it obvious to prepare the deuterated versions of the ethyl ester of levodopa. Levodopa is a well known drug that is widely utilized for treatment of neurological diseases including Parkinson's and restless leg syndrome. There is inherent motivation to improve on the bioavailability, activity and

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efficacy of the LDOPA and its prodrugs (ethyl ester is a known prodrug of LDOPA). Kushner teaches that such improvements can be attained by preparing deuterated versions of the known drugs.

In this regard, based on Kushner, those of ordinary skill would have been motivated to prepare those deuterated species that are instantly claimed, since these compounds would predictably have enhanced efficacy, activity, bioavailability and duration of action. Therefore, the instantly claimed deuterated compounds are prima facie obvious. Pharmaceutical compositions and the method of using the instant compounds are also obvious. One skilled in the art would find it obvious to use the deuterated variant of LDOPA prodrug to perform the same treatment as is already practiced with protonated variant.

Conclusion

Claims 1-10 and 34-38 are pending

Claims 1-10 and 34-48 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yevgeny Valenrod/

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